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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,169	11/28/2001	Lawrence Greenfield	07414.0022-01000	5874

7590 06/25/2002

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EXAMINER	
RILEY, JEZIA	

ART UNIT	PAPER NUMBER
1637	5

DATE MAILED: 06/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/997,169	GREENFIELD ET AL.	
	Examin r	Art Unit	
	Jezia Riley	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The art unit for this application has changed. Applicant is informed, that any future response should be directed to Art Unit 1637.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24, 41-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3, 4, 41 are vague and indefinite because it is unclear of what are the metes and bonds of the term "substantially".

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily

published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

4. Claims 1-6, 9-10, 14-17and 22-27, 30-33, 38-47, 52-55, 59, 60, and 64 are rejected under 35 U.S.C. 102(e) as being anticipated by Dattagupta et al. (US 6,242,188).

Dattagupta et al. describes compositions and methods for releasing nucleic acids from cells in a form that is suitable for labeling/capture, amplification, or detection in a single reagent addition step. The compositions include a lipid, membrane fluidizing compound, enzyme for degrading cell structure, metal chelators, or one or more nucleic acid probes or primers complementary to the nucleic acid to be detected. The compositions are non-denaturing and non-inhibitory of enzymes or proteins that are used in nucleic acid release, amplification, labeling or detection. The invention also provides kits for performing the above methods. The compositions for releasing nucleic acid include a lipid that can form liposomes or other structures under the appropriate conditions. Lipid used for the formation of the liposome can be natural or synthetic and include phospholipids, glycolipids, and lipid related compounds. Exemplary lipids include, lecithin (phosphatidylcholine), phosphatidylethanolamine, phosphatidic acid, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, sphingomyelin, cardiolipin, and hydrogenated derivatives thereof, which can be used either alone or in combination. The glycolipids include cerebroside, sulfolipid (e.g., sulfatide), and ganglioside. The structure of the liposomes may be as a multilamellar vesicle (MLV), a

small unilamellar vesicle (SUV), or large unilamellar vesicle (LUV). To stabilize the lipid, an antioxidant such as tocopherol (vitamin E) can be added to the solution. The liposome composition also can contain as a stabilizer, a high molecular weight polymer such as albumin, dextran, vinyl polymers, non-ionic surface active agents, gelatin, and hydroxyethyl starch. Liposomal vesicles that encapsulate aqueous solutions as used herein can be prepared by a variety of known methods. For example, conventionally used hydration, reversed phase evaporation, removal of surfactant, solvent injection, freeze-thawing and dehydration-rehydration can be employed. In the hydration method, the selected lipids are dissolved in an organic solvent (e.g., chloroform and ether), which is non-denaturing, and the solvent is evaporated from the resulting solution yield a thin homogeneous film. The aqueous solution containing, for example, an enzyme(s), a non-ionic membrane fluidizing compound(s), a metal chelator(s) or nucleic acid probes or primers is added to the thin membrane, and the mixture is subjected to agitation and sonication to yield a liposome preparation encapsulating the aqueous solution. The aqueous solution contains a buffer at a pH between 4 and 11. The pH of the buffer is chosen such that when the lipids or liposomes are added to an assay medium, the final pH in a range suitable to preserve nucleic acids in solution. In the reversed-phase evaporation method, the selected lipids are dissolved in an organic solvent (e.g., chloroform and ether), and are added to the aqueous solution and subjected to agitation, sonication and high pressure homogenization to uniformly disperse the aqueous solution. The solvent is evaporated from this dispersion to yield a liposome preparation encapsulating the aqueous solution. In the removal of surfactant

approach, the selected lipids dissolved in organic solvent are mixed with a surfactant (e.g., cationic surfactant such as cholic acid or deoxycholic acid, and a non-ionic surfactant such as Triton X-100 and octyl-D-glucoside) and added to the aqueous solution, which is followed by agitation, sonication and high pressure homogenization to uniformly disperse the aqueous solution. The surfactant is then removed by dialysis, gel filtration and ultrafiltration, which are applied singly or in combination. In the solvent injection, approach, the selected lipids are dissolved in organic solvent and are added to the aqueous solution, which has been set for a temperature about 10.degree. C. higher than the boiling point of the organic solvent. Then, the organic solvent is evaporated. The aqueous solution of the present nucleic acid releasing compositions also can include, for example, substances other than lipids that enhance release of nucleic acid depending on the nature of the sample and the environment in which the nucleic acid is contained (e.g., the type of cell). Such nucleic acid releasing substances include, for example, an enzyme(s) to degrade cell structure, a non-ionic membrane fluidizing compound(s), and/or a metal chelator(s). Enzymes suitable for use with lipid containing aqueous solution are available from natural sources or produced by recombinant DNA methods. Such enzymes include, for example, lysozyme, lipases, and proteinases such as proteinase K, pronase, trypsin and chymotrypsin. Lysozymes from bovine, chicken, human and lipases from wheat germ, human, yeast and other sources also are suitable enzymes to degrade cell structure. These enzymes preferably are nuclease free to support stability of released nucleic acids in solution. The aqueous solution containing lipids and enzymes for releasing nucleic acid can be encapsulated into a liposome, if

desired. Preferred lipids for use in the compositions and methods are cationic lipids (i.e., derivatives of glycerolipids with a positively charged ammonium or sulfonium ion-containing headgroup), including those useful in liposomal formulations for the intracellular delivery of negatively charged biomolecules such as oligonucleotides. The cationic lipid N-(1-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTMA") is a cationic lipid with an ammonium group that can be used in liposomal formulations present in the compositions of the invention. In such formulations, DOTMA may bind to DNA through an ionic lipid-DNA complex that assists in releasing nucleic acid from a cell. Other ammonium ion-containing cationic lipid formulations that can be used in the nucleic acid releasing compositions of the present invention include the DOTMA analog, 1,2-bis(oleoyloxy)-3(trimethylammonio)propane ("DOTAP") ; the lipophilic derivative of spermine; and cetyltrimethylammonium bromide. In the removal of surfactant approach, the selected lipids dissolved in organic solvent are mixed with a surfactant (e.g., cationic surfactant such as cholic acid or deoxycholic acid, and a non-ionic surfactant such as Triton X-100 and octyl-D-glucoside) and added to the aqueous solution, which is followed by agitation, sonication and high pressure homogenization to uniformly disperse the aqueous solution. The surfactant is then removed by dialysis, gel filtration and ultrafiltration, which are applied singly or in combination.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta et al. (6,242,188) in view of Van Ness et al. (5,130,423).

Dattagupta et al. describes compositions and methods for releasing nucleic acids from cells in a form that is suitable for labeling/capture, amplification, or detection in a single reagent addition step. The compositions include a lipid, membrane fluidizing compound, enzyme for degrading cell structure, metal chelators, or one or more nucleic acid probes or primers complementary to the nucleic acid to be detected (as discussed above).

Van Ness et al. discloses safe and effective methods for the extraction of nucleic acids. In particular, methods are described for isolating nucleic acid from a sample containing a biological mixture of nucleic acids and other biological compounds wherein the sample is combined with an extraction solution containing at least one organic compound such as benzyl alcohol or a benzyl alcohol derivative to form an aqueous and non-aqueous phase. The nucleic acid is isolated from the aqueous phase. Preferably, the resulting combined solution also contains bentonite. Typically, the sample will first be combined with a lysing agent before extraction. The lysing agents preferred are chaotropic salts such as guanidinium hydrochloride and guanidinium isothiocyanate.

Therefore it would have been obvious at the time the invention was to nucleases inhibitor such as bentonite as taught by Van Ness for the method of Dattagupta. The motivation is that this extraction protocol allows the isolation of nucleic acids from particularly complex samples lysed with guanidinium isothiocyanate without the use of phenol or phenol/chloroform. The organic phase is composed of benzyl alcohol and bentonite. Phenol or a phenol/chloroform mixture is corrosive to human skin and is considered as hazardous waste, which must be carefully handled and properly discarded. Further, the extraction method is time consuming and laborious. Further, the use of chaotropic agents such as guanidinium thiocyanate (GnSCN) are widely used to lyse and release nucleic acid from cells into solution, largely due to the fact that chaotropic salts inhibit nucleases and proteases. However, it has proved difficult to isolate the nucleic acids from these chaotropic salt solutions due to the incompatibility of the chaotropes with ionic detergents and the inability to easily partition the nucleic acid into an aqueous phase, given the use of such high molar concentrations of salt. The ability to effectively inhibit nucleases during nucleic acid isolation procedures is paramount, especially when the starting material is complex, such as feces or blood. Researchers reported the use of bentonite in combination with phenol and chloroform in the reduction of ribonuclease activity during the isolation of RNA. It has also been reported that DNase 1 and alpha-amylase can be made RNAse-free by treatment with bentonite.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jezia Riley whose telephone number is 703-305-6855. The examiner can normally be reached on 9:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Patent Anal;yst Monica Graves whose telephone number is 703-305-3002 or to the Technical Center receptionist whose telephone number is 703-308-0196.

June 24, 2002

JEZIA RILEY
PRIMARY EXAMINER